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# Fine Motor and Handwriting Problems After Treatment for Childhood Acute Lymphoblastic Leukemia

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Motor skills were investigated in 18 children 2 years after treatment for acute lymphoblastic leukemia (ALL). Gross and fine motor functioning were examined with the Movement Assessment Battery for Children. Handwriting as a specific fine motor skill was studied with a computerized writing task. We conclude that 2 years after cessation of treatment motor problems in ALL survivors were still present. Dysfunctions were mainly pronounced in handwriting and fine motor skills. 

**Key words:** late effects, acute lymphoblastic leukemia, vincristine neuropathy, children, fine motor problems, handwriting problems

## INTRODUCTION

Children with acute lymphoblastic leukemia (ALL) often develop impaired motor functioning *during* treatment. Among these are loss of deep tendon reflexes, paresthesias, weakness, gait disturbance, clumsiness, and loss of fine motor control with poor handwriting. These signs and symptoms may be part of vincristine-induced neuropathy [1–3], but other neurotoxic side effects of treatment cannot be excluded. Most of the unwanted neurotoxic effects are thought to disappear gradually after cessation of treatment, but measurement of fine motor skills as part of neuropsychological assessment in children who survived ALL suggested *long lasting* motor problems [4–8,14] especially interfering with writing skills and therefore with school performance [6]. Motor functioning, particularly a complex motor skill like handwriting, depends on proper central nervous system (CNS) functioning. Most of the above-mentioned neuropsychologic studies concerned children with cranial irradiation as presymptomatic CNS treatment, and this treatment modality has caused prolonged CNS damage especially in young children [15].

So far only one study has addressed motor function in children who survived ALL but did not receive cranial irradiation [14]. Therefore, we studied children whose presymptomatic CNS treatment consisted of high-dose methotrexate and repeated intrathecal therapy instead of cranial irradiation. Their gross and fine motor skills at least 2 years after cessation of treatment are reported using the Movement Assessment Battery for Children (Movement ABC) and a computerized writing task.

## PATIENTS AND METHODS

### Patients

Children treated for ALL with chemotherapy including vincristine were eligible for the study if at the time of assessment they were off treatment at least 2 years, 7 years or older (to be able to perform the writing task), and attending regular school. After written informed consent from their parents 9 boys and 9 girls were studied 2.02–7.11 years. months (mean 4.00) after treatment for ALL. Their ages ranged from 2.04 to 8.02 (mean 4.03) years at diagnosis and from 7.10 to 12.05 (mean 10.03) years at the time of motor assessment. The children were treated according to consecutive Dutch Childhood Leukemia Study Group (DCLSG) protocols VI (n = 9) [21] and VII (n = 9) [16]. No cranial irradiation was involved. Children treated according to protocol VI received significantly higher cumulative doses of vincristine than children treated according to protocol VII ($22 \times 2$ and $4 \times 1.5$ mg/m$^2$/gift, respectively; capped at 2.5 and 2.0 mg vincristine gift, respectively). All children were in continuous complete remission. The test results were compared with those of 18 age- and sex-matched healthy controls (Table I).

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**TABLE I. Age at Different Moments of Leukemia and Control Group**

| | Leukemia (n = 18) | | Controls (n = 18) | |
|---|---|---|---|---|
| | Mean (yr.mo)[a] | Range (yr.mo) | Mean (yr.mo) | Range (yr.mo) |
| Age at test moment | 10.03 | 7.10–12.05 | 10.01 | 7.05–12.04 |
| | ALL-6 (n = 9) | | ALL-7 (n = 9) | |
| | Mean (yr.mo) | Range (yr.mo) | Mean (yr.mo) | Range (yr.mo) |
| Age at diagnosis | 3.05 | 2.04–4.09 | 5.02 | 3.03–8.02 |
| Age at test moment | 10.10 | 8.04–12.03 | 9.08 | 7.10–12.05 |
| Time off treatment | 5.02 | 2.10–7.11 | 2.10 | 2.02–3.10 |

[a]Years.months.

## Methods

Global motor functioning was tested using the Movement ABC [9]. This test measures 8 items grouped in 3 subtests: manual dexterity, ball skills, and static and dynamic balance. The Movement ABC is an internationally acclaimed instrument for diagnosis of delays or deficits in motor development. The Total Impairment Score is obtained by summation of the scores on all separate items, a higher score meaning worse motor performance. Total Impairment Scores below the 5th percentile are considered indicative of a definite motor problem. Scores between the 5th and 15th percentiles suggest a borderline difficulty.

A computerized writing task (Fig. 1) was used to study the handwriting of the children. This task is an instrument to acquire objective data about kinematic parameters of the writing movement. This equipment has been used previously as a computerized drawing task [10]. Briefly, children were seated at a distance of 0.8 m in front of a video screen randomly displaying 8 words per writing task (Fig. 2). The complexity of the words differed in number of movement elements: 3 or 6 letters. Each test included 4 tasks. The children were asked to copy the displayed words using a ball pen flexibly connected to a computer onto a sheet of paper placed on an XY digitizer. The use of an XY digitizer enables recording of writing in terms of horizontal and vertical coordinates at a sampling rate of 142 Hz and a spatial accuracy of 0.1 mm.

The following variables were calculated:

1. Movement time (MT), measured as the sum of the separate upward and downward stroke durations without pauses at the top of a letter and between letters.
2. Movement fluency (FL), which is the number of absolute velocity inversions made during writing of the single strokes; a velocity inversion is defined as an acceleration phase followed by a deceleration phase.
3. Pause duration (PD), which is the sum of duration of pauses at the top of a letter and between letters; a pause is defined as a period near zero velocity at the top of a letter and between letters (Fig. 3).

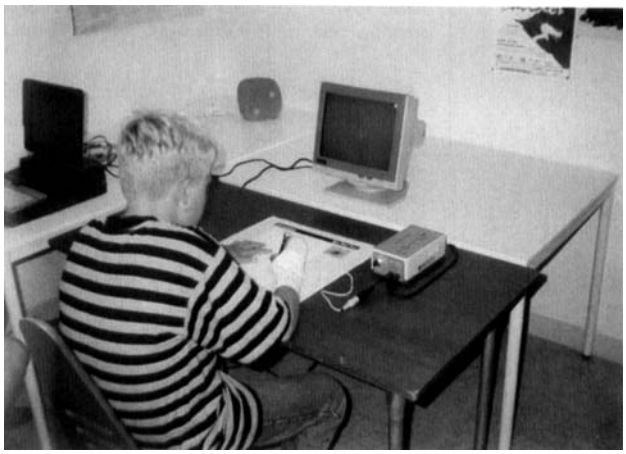

**Fig. 1.** Computerized writing task.

bal
ballen
bak
bakken
bel
bellen
bek
bekken

**Fig. 2.** Eight writing words (Dutch): bal = ball, ballen = balls, bak = box, bakken = boxes, bel = bell, bellen = bells, bek = mouth, bekken = mouths.

## Statistical Analysis

Results of ALL survivors on the Movement ABC were compared to their controls using a Mann-Whitney U-test. The other variables of the computerized writing task were analyzed using a 2 (group) with covariance (age at test) MANOVA. Z-scores were calculated using the formula:

$$z = (x - \mu)/\tilde{O}$$

Fig. 3. Start and endpoints of the writing strokes. /: Start and endpoint of the word. //: Pause duration after a writing stroke.

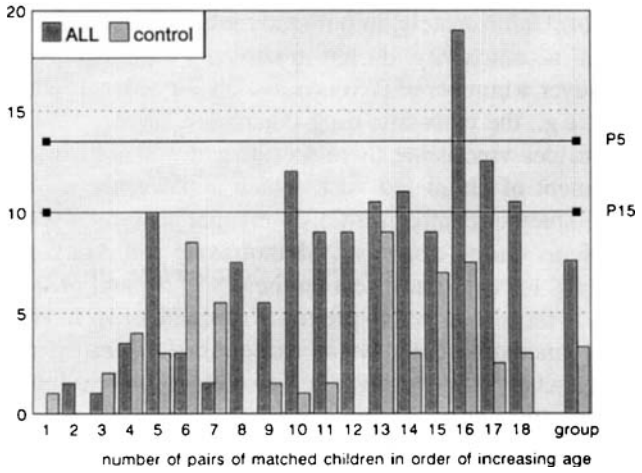


Fig. 4. Movement ABC, Total Impairment Score; no bar means score = 0.

Where x indicates a measurement result in a leukemia survivor, μ denotes the mean of the measurement in the reference population, i.e., the control group, and Õ denotes the standard deviation (SD) of the measurement in this reference population.

## RESULTS

### Movement ABC

Leukemia survivors performed worse on total test score ($P < 0.01$). Compared to normative data 6 survivors scored below the 15th percentile (Fig. 4). When we examined the differences on subtests of the Movement ABC, a significant difference between survivors and controls was obtained for manual dexterity ($P < 0.01$), survivors performing worse on manual dexterity. Compared to normative data 4 survivors scored between the 5th and 15th percentiles; 3 other survivors scored below the 5th percentile (Fig. 5).

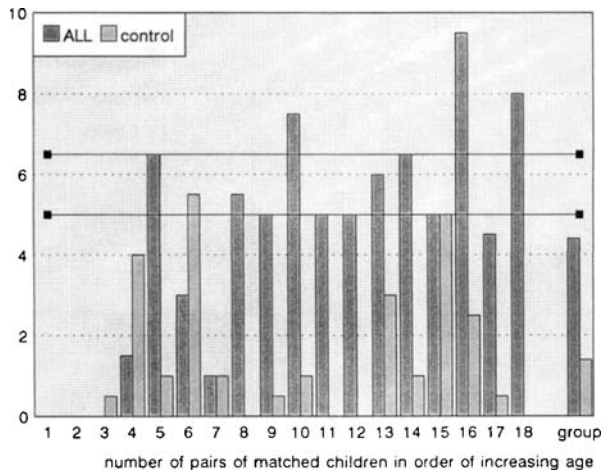


Fig. 5. Movement ABC, manual dexterity; no bar means score = 0.

### Writing Task

Seventeen leukemia survivors and 17 controls were included in the analyses of the writing test. One control was excluded due to outliers and influential data points.

First the differences (DIF) between 3- and 6-letter words on movement time (MTDIF), fluency (FLDIF), and pause duration (PDDIF) were measured. Using univariate and multivariate analyses no significant differences were found between the leukemia survivors and the controls when evaluating writing words of different complexity, i.e., 3- and 6- letter writing words. This did not change when corrected for age at time of measurement.

A summation (SUM) of the scores on 3- and 6- letter writing words was analyzed. Without correction for age at time of measurement, a multivariate group difference was found but after correction for age the data were shown to be much more complicated. The score on pause duration (PDSUM) was dependent on age at time of measurement. The children treated for ALL used significantly longer pauses during writing and the difference between the younger leukemia survivors and the control group was significantly more pronounced than the difference between the older leukemia survivors and the older controls. Interdependency between age at time of measurement and group was found for the scores on movement time (MTSUM) and fluency (FLSUM). The regression lines for these test parameters did cross. This means that at a younger age the leukemia survivors used more movement time and wrote more dysfluently than the younger controls but at an older age the reverse was found. Concerning individual results on MTSUM, PDSUM, and FLSUM, 4, 3, and 5 patients deviated more than 2 SD from the mean value of the control group, respectively. They used longer movement times, more pause durations, and wrote more dysfluently (Fig. 6). Overall the test results suggest that approximately 25% of the leukemia

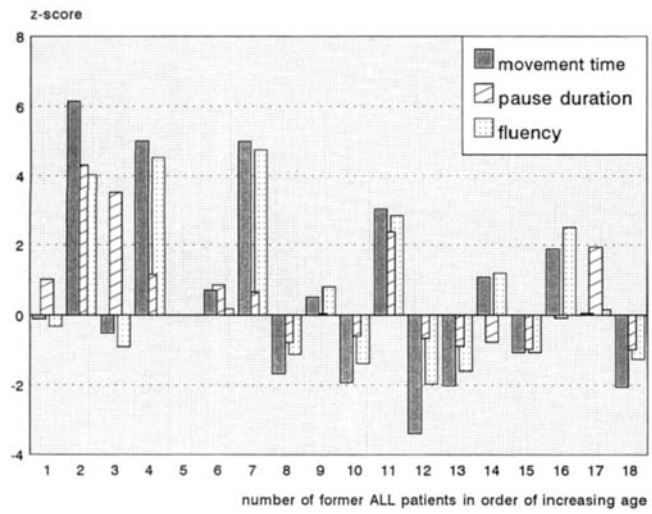


**Fig. 6.** Writing task: z-scores of movement time, pause duration, and fluency. Patient 5 was excluded.

survivors show handwriting problems more than 2 years after treatment. No significant differences were found on any of the variables between leukemia survivors treated with high (DCLSG protocol ALL-6) or low (DCLSG protocol ALL-7) cumulative vincristine doses.

## DISCUSSION

Leukemia survivors in our study still showed fine motor problems 2 years or more after cessation of treatment for ALL. This is in accordance with the study of Vainionpää [14], who used different motor assessment tools but also found fine motor disorders in 33% of patients treated for ALL without cranial irradiation 2–3 years after therapy. Handwriting is seen as a specific fine motor skill, but we could not show significant group differences for handwriting variables between children treated for ALL and age- and sex-matched controls. However, considering individual handwriting results, 6 of the 17 leukemia survivors do have handwriting problems. Comparing the individual data of the Movement ABC with the handwriting task, all children but one who had fine motor problems do not have handwriting problems and vice versa. Altogether two thirds of the former ALL patients have either fine motor or handwriting difficulties. So although handwriting is often seen as a fine motor skill, it is worth testing apart other fine motor skills. This can be supported by the specificity hypothesis of Henry [19]. Two tasks that look very similar can appeal to different abilities, which are needed to perform different tasks.

The wide age range at testing from 7 to 12 years old may have complicated the handwriting results, because in this age span a change of handwriting features is known. In addition, the developmental pace in handwriting is not necessarily the same for writers of high and low proficiency according to Smits-Engelsman et al. [11]. Children suffering from motor problems due to neuropathy at an early age may therefore have chosen different and more or less successful strategies to overcome their problems.

A remarkable crossing of regression lines was found for the scores on movement time and fluency of handwriting related to age of ALL survivors and controls at time of measurement. We have no explanation for this apparent interdependency between age at time of measurement and group. Because we did not find a statistically significant interdependency, this finding is probably due to small sample size. Larger numbers have to be investigated before firm conclusions can be drawn.

An important question is why some patients suffer from neurotoxicity during and after treatment while others do not. Unfortunately, in our study no retrospective data about neurotoxicity during treatment were available. However, a number of factors is associated with neurotoxicity, e.g., the cytostatic drug vincristine [1–3].

Besides vincristine there are other drugs used in the treatment of childhood ALL which could cause neurotoxic (methotrexate, Ara-C) or myopathic (prednisone) problems during treatment. Methotrexate and Ara-C reportedly have a toxic effect on the CNS [20] and prednisone is mostly related to proximal myopathy [3]. In contrast, vincristine is known to cause a distal sensory and motor neuropathy. Because the fine motor problems found in our study are probably more of a peripheral nature, we suggest a possible causative role of vincristine.

Our study group differed with regard to cumulative dose of vincristine as well as age at treatment and time lapsed since treatment. In addition, a large variation in systemic exposure to vincristine between individuals has recently been reported [17]. No group differences were found on any of the motor variables between the children treated with high (ALL-6) or low (ALL-7) cumulative doses of vincristine. Hence, a causal relation with vincristine dose could not be demonstrated, but this may be due to the small sample size. Also, other factors such as individual differences in time after treatment may be important. In order to elucidate the relationship between vincristine, neuropathy, and motor problems during and after treatment, we have started a prospective longitudinal study in children with ALL, concurrent with a second study on pharmacokinetic and pharmacodynamic effects of vincristine. This may be particularly important because McHale and Cermak [18] revealed that 30–60% of daily school activities deal with fine motor skills, writing tasks predominating other manipulative tasks. When children have either a general problem with manual control or a difficulty confined to graphic skills, their academic school performance will be limited and therefore frustrating [9]. Because the persisting fine motor and handwriting prob-

lems are rather diverse, individualized rehabilitation programs may be needed.

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